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Regional Alterations in Blood-to-Brain Transfer of α-Aminoisobutyric Acid and Sucrose, After Chronic Administration and Withdrawal of Dexamethasone

Y. Z. Ziylan, J. M. Lefauconnier, G. Bernard, and J. M. Bourre

Unité de Neurotoxicologie, INSERM U. 26, Hôpital Fernand Widal, Paris, France

Abstract: The effect of dexamethasone administration and withdrawal was studied with respect to blood–brain barrier function. The tracers α-[^{3}H]aminoisobutyric acid (AIB) (MW 104) and [^{14}C]sucrose (MW 342), which have a low permeability across the intact endothelium, were simultaneously injected intravenously in rats treated with dexamethasone and placebo-treated control animals or in rats in which dexamethasone treatment was discontinued 3 days before the experiment. Unidirectional transfer constants (K_i) were determined in discrete brain regions. Steroid administration reduced the rate of influx of AIB and sucrose, whereas discontinuation of drug resulted in an increased permeability. These findings suggest that when exposure to glucocorticoids is prolonged, the efficiency of medical treatment of CNS diseases may decrease due to reduction of drug delivery to CNS. Thus, these experimental findings may have particular importance in the clinical setting of drug administration when considering the combination of steroids with other drugs, and may aid in understanding better the pathogenesis of some types of brain edema seen in patients from whom corticosteroid therapy has been withdrawn. **Key Words:** Blood–brain barrier—Dexamethasone—Cerebrovascular permeability—Glucocorticoids—CNS. **Ziylan Y. Z. et al.** Regional alterations in blood-to-brain transfer of α-aminoisobutyric acid and sucrose, after chronic administration and withdrawal of dexamethasone. *J. Neurochem.* **52,** 684–689 (1989).

Glucocorticoids (GCs) are now widely used in neurological and neurosurgical practice. There have been several clinical studies indicating the beneficial effect of steroids in relieving certain neurological conditions, the mechanism being generally attributed to a reduction in brain edema (Galicich et al., 1961; Rasmussen and Gulati, 1962; Weinstein et al., 1973; Fishman, 1982). Numerous studies have demonstrated that dexamethasone (DXN) reduces experimentally increased cerebrovascular permeability. Administration of GCs repairs the damage in the blood–brain barrier (BBB) caused by hypertension (Bloomstrand et al., 1975; Johansson, 1978; Hansson and Johansson, 1979; Ziylan et al., 1984*a*), repeated convulsions (Eisenberg et al., 1970; Sztriha et al., 1986), ethanol toxicity (Rosengren and Persson, 1979), tumor (Shapiro and Posner, 1974; Yamada et al., 1979; Matsuoka and Hossmann, 1981; Reichman et al., 1986), cerebral infarction and hypoxia (Fenske et al., 1979; Barbrosa-Coutinho et al., 1985), and osmotic BBB injury (Neuwelt et al., 1982), thereby reducing the induced permeability increase. It has also been shown that DXN lowers the normal permeability of brain vessels to horseradish peroxidase (HRP) in mice (Hedley-Whyte and Hsu, 1986) and permeability surface area product (*PA*) for water in the cerebral cortex of rats (Reid et al., 1983*a,b*).

Furthermore, Long and Holaday (1985) have recently reported that bilateral adrenalectomy but not adrenal medullectomy increased the penetration of labelled bovine serum albumin into brain, and this effect

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Address correspondence and reprint requests to Dr. Y. Z. Ziylan at INSERM U.26, Hôpital Fernand Widal, 200 rue du Faubourg Saint Denis, 75475 Paris Cedex 10, France.

The permanent address of Dr. Y. Z. Ziylan is Department of Physiology, Istanbul Faculty of Medicine, CAPA-34390 Istanbul, Turkey.

Abbreviations used: ACTH, adrenocorticotrophic hormone; AIB, α-aminoisobutyric acid; BBB, blood–brain barrier; CBF, cerebral blood flow; DXN, dexamethasone; GC, glucocorticoid; HRP, horseradish peroxidase; *PA*, permeability surface area product.